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Polymer excipients enable sustained drug release in low pH from mechanically strong inorganic geopolymers

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ABSTRACT

Improving acid resistance, while maintaining the excellent mechanical stability is crucial in the development of a sustained and safe oral geopolymer dosage form for highly potent opioids. In the present work, commercially available Methacrylic acid–ethyl acrylate copolymer, Polyethylene-glycol (PEG) and Alginate polymer excipients were included in dissolved or powder form in geopolymer pellets to improve the release properties of Zolpidem, herein acting as a model drug for the highly potent opioid Fentanyl. Scanning electron microscopy, compression strength tests and drug release experiments, in gastric pH 1 and intestinal pH 6.8 conditions, were performed. The polymer excipients, with an exception for PEG, reduced the drug release rate in pH 1 due to their ability to keep the pellets in shape, in combination with the introduction of an insoluble excipient, and thereby maintain a barrier towards drug diffusion and release. Neither geopolymer compression strength nor the release in pH 6.8 was considerably impaired by the incorporation of the polymer excipients. The geopolymer/polymer composites combine high mechanical strength and good release properties under both gastric and intestinal pH conditions, and are therefore promising oral dosage forms for sustained release of highly potent opioids.

1. Introduction

Controlled and sustained release of drugs is important for patients requiring medicinal treatment around the clock. One such example is cancer patients with chronic or persistent pain given very potent opioids, such as Fentanyl [1,2,3]. However, because of the high potency and narrow therapeutic window of these drugs, even small variations in plasma concentrations could lead to severe side effects [4]. As a consequence, when formulating potent drugs into sustained release dosage forms, it is of special importance to have control over the drug release profile and thus also the drug absorption. Geopolymers have recently been suggested [5,6] for controlled and safe release of highly potent opioids due to their mechanical and chemical integrity. This class of materials has mainly been suggested to replace Portland cement as a construction material due to the lower energy required in its preparation [7]. Geopolymers are formed in a dissolution and precipitation process using aluminosilicate precursor materials, such as thermally treated kaolin, in alkaline media and silicate solutions [8]. The final product consists of an amorphous three dimensional network of tetravalent silica and alumina species with the charge compensating single valent cations, e.g. Na^+. The water used in synthesis is expelled during reaction to form the pores after drying [7,8]. Geopolymers with different microstructure may be formed by varying the aluminosilicate precursor type [7], the stoichiometric ratio of silica [9], the alkali hydroxide and water contents [10] as well as the reaction temperature and pressure [7].

Using pore-network modeling and characterization, we have shown that it is possible to tune the porous geopolymer microstructure and the resulting molecular diffusion coefficients of drugs incorporated in this structure to span over two orders in magnitude [10]. It has also been shown that Fentanyl was released at a considerably higher rate under low pH conditions (pH 1; mimicking acidic stomach conditions) as compared to neutral pH (pH 6.8 mimicking small intestine conditions), which was partly related to the higher solubility of Fentanyl at low pH [5]. Apart from an increased drug solubility at low pH, geopolymer degradation was also believed to be a contributing cause of the increased Fentanyl release rate [5], a problem that is also present for other clay-based delivery vehicles [11]. Geopolymers are depolymerized [7] in acidic media in a process where the charge balancing cations (Na^+) in the geopolymer framework are

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replaced by H^+ or H_3O^+ ions from the solution along with an electrophilic attack by acid protons on the polymeric silalate Si–O–Al and siloxo Si–O–Si bonds. The ejection of tetrahedral alumina and silanol species have been observed [12] to be followed by immediate formation of new phases, such as zeolites and gypsum crystals [7,13].

The aim of the work is to investigate the influence of incorporating different polymer excipients in pellets made of one geopolymer formulation on the mechanical strength as well as on the release behavior of Zolpidem from the same. Zolpidem is chosen as the model drug in this study due to safety considerations during handling; it is considerably less potent than the physico-chemically similar and highly potent Fentanyl [5].

2. Materials and method

2.1. Materials

Kaolin ($Al_2Si_2O_5(OH)_4$), fumed silica (SiO_2, 7 nm particle size), reagent grade sodium hydroxide (NaOH) (Sigma-Aldrich, Stockholm, Sweden) and Zolpidem tartrate ($C_{19}H_{21}N_3O$, Cambrex AB, USA) were used as received. The investigated polymer excipients were Kollicoat MAE 100P (BASF, Luwigshafen, Germany), Poly(ethylene glycol) (#81300, Sigma-Aldrich, Stockholm, Sweden), Protanal L10/60 and L10/60 LS with a high ($G_c \approx 70\%$) and low ($G_c \approx 40\%$) guluronic acid content G_c, respectively (kindly donated by the FMC biopolymer, Norway). In addition, the polymer excipient Eastman CAP (Eastman Chemical Company, USA) was briefly tested and discarded. Important polymer excipient characteristics are as summarized in Table 1.

2.2. Methods

2.2.1. Synthesis

Metakaolin ($Al_2O_3 \cdot 2SiO_2$) was initially prepared by thermal treatment of Kaolinite at 800 °C for 2 h. Sodium silicate solution (waterglass) was prepared by mixing sodium hydroxide, fumed silica and de-ionized water until a clear and viscous solution was formed. A geopolymer paste ($Si/Al = 1.77$, $Na_2O/Al_2O_3 = 1.4$, $H_2O/Al_2O_3 = 14$) was prepared by mixing metakaolin, waterglass and the model drug Zolpidem tartate without (Control) or with 1 g of polymer excipient in dissolved or powder form per 6.5 g Metakaolin in a glass mortar until a uniform paste was formed. The paste was molded in cylindrically shaped Teflon® molds resulting in pellets of the size 1.5 mm × 1.5 mm (diameter × height) and in rubber molds resulting in rods for compression strength tests with a corresponding size of 6 mm × 12 mm. The geopolymer precursor was cured at 37 °C for 48 h in 100% relative humidity (RH) and stored in an 11% RH dessicator before analysis. The pellets prepared from pastes containing polymers in dissolved form and powder form were named after the polymer used with the extension D or P, respectively. In addition to the samples named Control, Ko D, Ko P, PEG D, Alg-G P and Alg-M P, samples made from geopolymer pastes containing only half the amount of powder form Kollicoat and PEG (i.e. 0.5 g of excipient per 6.5 g of Metakaolin); viz. Ko-h P and PEG-h D, were prepared. Compositions with pre-dissolved Alginate (Alg-G D and Alg-M D) were prepared, but discarded as alginate degraded in the caustic synthesis environment [14]. PEG P samples were also prepared, but the PEG powder did not homogenously mix into geopolymer paste, which therefore was discarded.

2.2.2. Scanning electron microscopy (SEM)

The SEM micrographs of fracture surfaces of the pellets were taken with a Leo 1550 FEG microscope (Zeiss, UK) equipped with an in-lens detector. A thin gold/palladium layer was sputtered onto the fracture surfaces of the non-conducting samples prior to analysis to minimize charging of the samples. The analysis was performed with 5 kV acceleration voltage.

2.2.3. Compression strength

The compression strength of each composition ($n = 7$) was measured as the maximum pressure that could be applied on the 6 mm × 12 mm rods before breakage using an Autograph AGS-H universal testing equipment (Shimadzu Corp., Japan).

2.2.4. Drug release measurements

Zolpidem release from the pellets was evaluated in a USP-2 dissolution bath (Sotax AT7 Smart, Sotax AG, Switzerland) equipped with 1000 ml vessels (37 °C, 50 rpm). 400 mg of pellets were placed in each vessel containing 400 ml of either phosphate buffer set to pH 6.8 or 0.1 M HCl, pH 1. In all experiments the quantities of pellets corresponded to a drug amount below 10% of the drug solubility in order to ensure that sink conditions always prevailed. Aliquots (1 ml) were manually withdrawn at different time points during the release, and the concentration of drug in these samples was analyzed with a UV/VIS photo-spectrometer (Shimadzu 1800, Japan). Any possible interference of dissolved polymer excipients in the drug absorbance/concentration measurements was evaluated by separately dissolving the polymers in the relevant buffer solutions. The absorbance of the polymers was found to be considerably lower than for the Zolpidem drug at its absorption peaks (241 and 300 nm). A photograph (Cybershot DSC-HX100V, Sony Corp., Japan) of the bottom of each dissolution vessel was taken after 6 h of drug release in pH 1. The drug release was studied for 6 h in pH 1 and for 24 h in pH 6.8. These total release times were chosen to mimic in vivo residence time of the pellets in the stomach and the intestinal tract.

3. Results and discussion

3.1. Pellet microstructure

Fig. 1 shows SEM micrographs of typical fracture surfaces of geopolymer pellets samples without added polymers (panel a) as well as samples of the same geopolymer composition with polymers incorporated (panels b–f). The geopolymer sol–gel reaction allows pellets of any size and shape to be synthesized. When mixing the pre-heated kaolinite in the alkaline waterglass, the kaolinite is dissolved, forming reactive Si- and Al-species that

Table 1
Polymer excipient specifications.

Trade name	Base compound/chemical name	Abbreviation	Soluble in pH
Kollicoat MAE 100P	1:1 Methacrylic acid/ethyl acrylate	Ko	> 5.5
Polyethylene glycol	Polyethylene glycol (MW 20 k)	PEG	Solubility is pH independent
Protanal LF10/60	Alginic acid ($G_c \approx 70\%$)	Alg-G[a]	> 4.0
Protanal LF10/60 LS	Alginic acid ($G_c \approx 40\%$)	Alg-M[b]	> 4.0

[a] G denotes a higher ratio of guluronic acid.
[b] M denotes a higher ratio of manuronic acid.

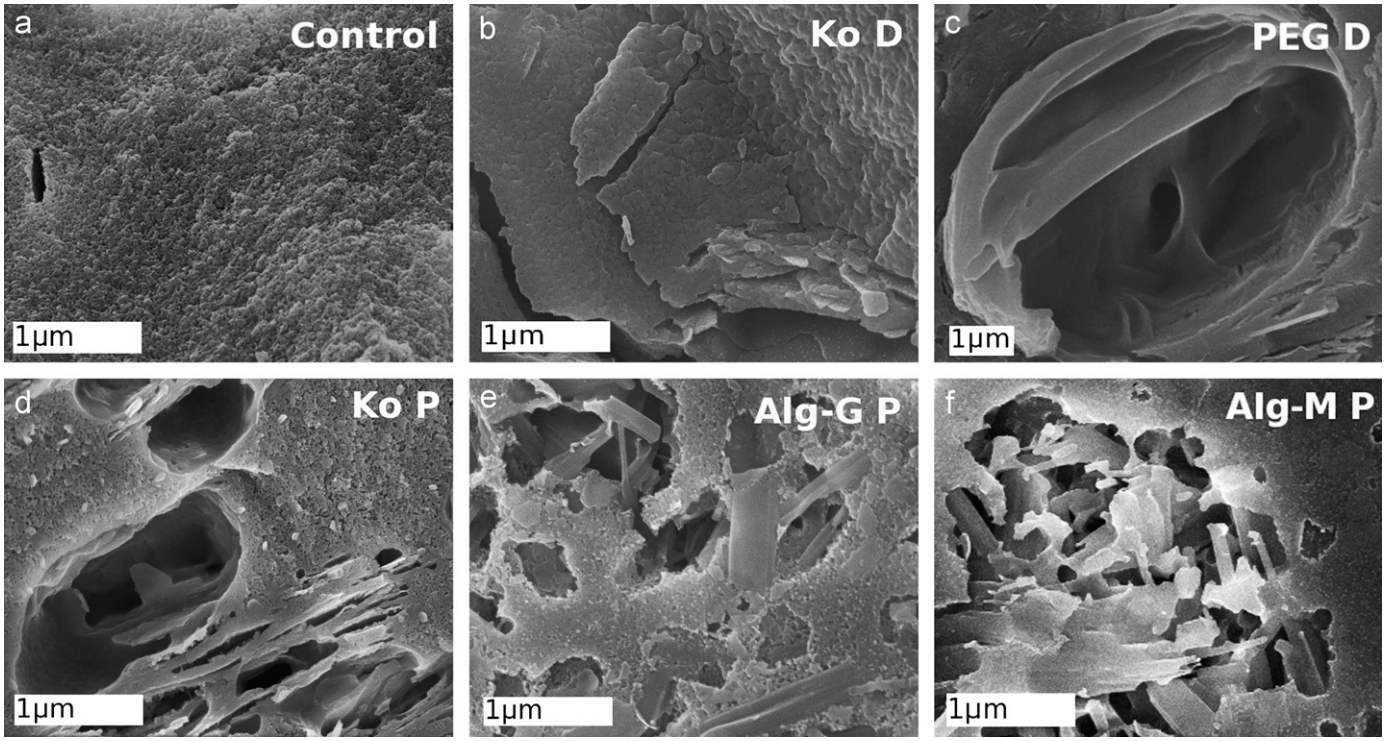

Fig. 1. SEM micrographs of geopolymer without polymers added (a) as well as with added polymer excipients in dissolved (b, c) or powder (d–f) form.

precipitate via nucleation and growth into a nanoparticulate meshwork of clusters [7], as can be observed in Fig. 1a. It should be noted that the diameter of native pores for similar geopolymer composition ($Si/Al = 1.77$, $Na_2O/Al_2O_3 = 1.4$, $H_2O/Al_2O_3 = 14$) has been found to be in the 10–20 nm range, [10] which is in conformity with the pores observed upon a closer inspection of the Control sample in Fig. 1a.

Adding pre-dissolved methacrylic acid/ethyl acrylate copolymer in the geopolymer paste during synthesis resulted in a fairly homogeneous distribution of polymer in the geopolymer structure without evident signs of lumps of aggregated polymer, cf. Ko D, Fig. 1b. Conversely, the use of pre-dissolved PEG in synthesis resulted in larger polymer bundles (~6 µm, cf. Fig. 1c) as observed by SEM, despite that no phase separation was seen during synthesis. Both the commercially available Kollicoat MAE 100P and PEG dissolved in 2 M NaOH and formed a clear solution prior to synthesis. However, adding Kollicoat in powder form during synthesis resulted in micrometer-sized voids (~1 µm) in the geopolymer pellet structure with the smooth polymer covering the interior void surfaces (sample Ko P) as evident from Fig. 1d. The same type of voids was found in the structure of geopolymer pellets containing powder form Alg-G and Alg-M, cf. Fig. 1e–f. Hence, the voids are most likely footprints after larger powder particles that have dissolved and created a polymer layer on the surface of the walls surrounding the voids while the voids created in the PEG sample (Fig. 1c) are likely caused by a phase separation. The polymer layer obviously also penetrated the native pores of the geopolymer structure neighboring the voids as indicated by the smooth structure at a distance of ≤ 0.5 µm from the voids (Fig. 1c–f) in the otherwise rather particulate geopolymer fracture surface. In Fig. 1a–d, elongated voids are visible, and are most likely stemming from unreacted metakaolinite sheets ripped off during the SEM sample preparation process. The incorporated Zolpidem was not observed in SEM due to the low drug content (~0.75 vol%).

3.2. Compression strength

Fig. 2a shows the measured compression strengths of the samples under study. It can be observed that the samples prepared with polymers in powder form had lower compression strength than the pure geopolymer Control sample and the samples synthesized with pre-dissolved polymers. The Alg-G P and Alg-M P samples had compression strengths that were statistically significant lower than the Control, the Ko D and the Ko h D samples, whereas the PEG D samples had a compression strength that was significantly lower than the Ko h D sample but with an average value lower than both Ko D and Control.

The compression strength of a material depends on how much compression load per area the microstructure of a material can withstand before collapsing. Porous solids display lower compression strengths than their non-porous counterparts due to the reduction of load-bearing solid material in the former. Inhomogeneities, naturally found in the pore structure or formed via inclusion of foreign materials (e.g. polymer), may create stress concentrations in the structure when a compressive force is applied. When the maximum local stress that the structure can withstand is exceeded, a crack forms that eventually propagates, and leads to material breakage. More and larger structural inhomogeneities generally increase the probability of crack formation; thus, the compression strength is proportional to size and density of defect sites [15]. A sufficiently well dispersed polymer, i.e. only residing in the native geopolymer pores, might conceivably even reduce the overall sample porosity, and increase compression strength of the material. The measured compression strengths for Ko D and Ko-h D were, however, not found to be statistically significantly different from the Control sample although the average value for the Ko h D sample was somewhat larger.

The somewhat lower compression strengths of the samples synthesized with polymers in powder form for the alginates and solution form for PEG are most probably caused by a higher

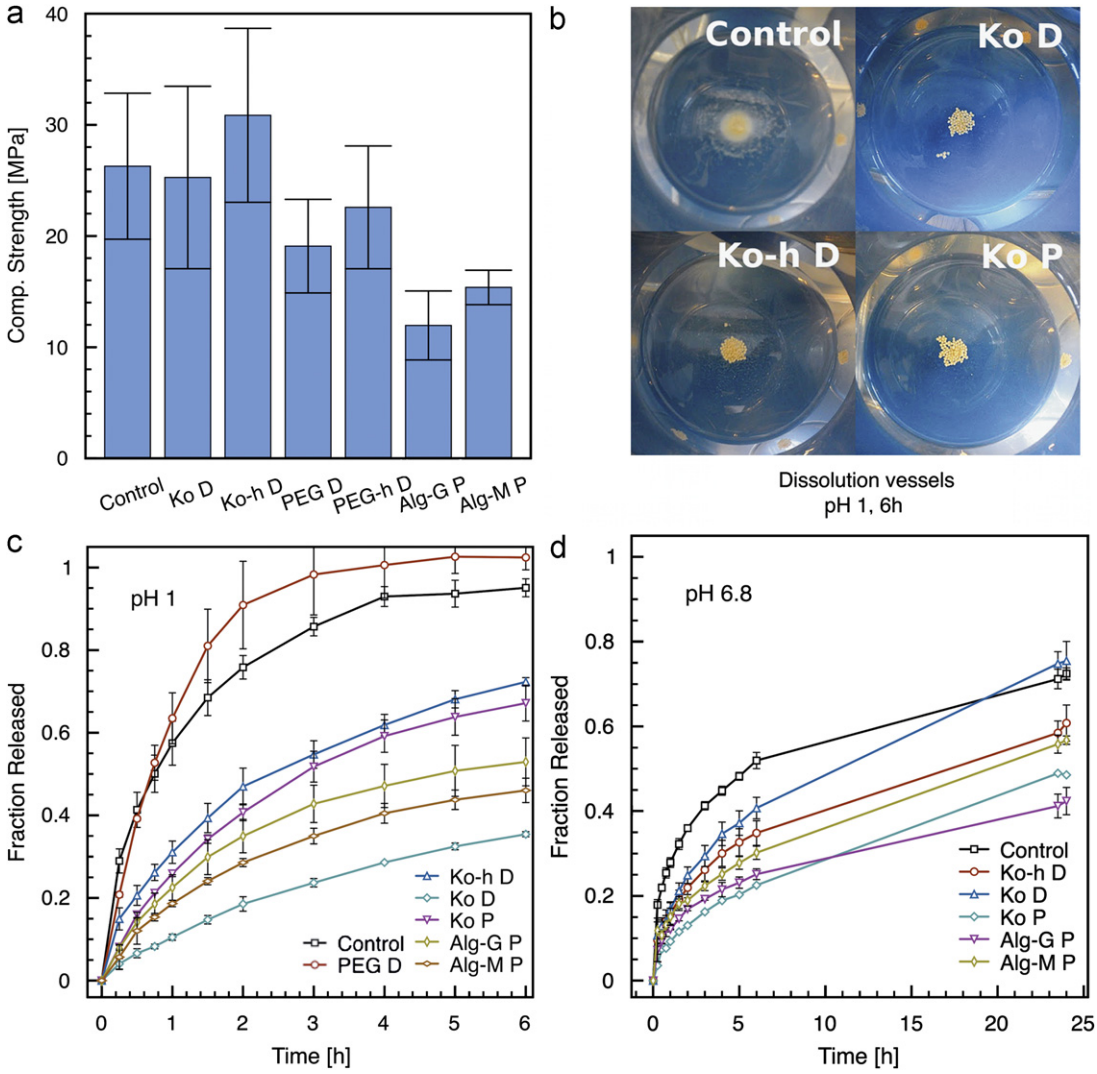

Fig. 2. Compression strength data with error bars denoting standard deviation of at least 7 rods (a). Photograph of pellets on the bottom of the dissolution vessel after 6 h in pH 1 (b). Zolpidem release in pH 1 (c) and pH 6.8 (d) dissolution media. The data points and error bars denote averages and standard deviations from 3 consecutive measurements.

fraction of structural defects, such as the micrometer-sized voids observed in SEM (Fig. 1c–f), which are expected to weaken the overall mechanical stability of the matrix as reasoned above. Reducing the amount of added polymer (compare PEG-h D and PEG D) thus leads to increased compression strength.

3.3. *Drug release*

Fig. 2b shows photographs of a selection of pellets at the bottom of the USP-2 dissolution vessels after 6 h of release in pH 1. Pellets containing polymer excipients insoluble in pH 1 (i.e. Ko, Alg-G and Alg-M, cf. Table 1) were observed to maintain their shape during release, whereas PEG D (not shown in the figure) and Control sample pellets eroded into fine grains within a few hours of release in low pH. Comparing the pellet containing methacrylic acid/ethyl acrylate copolymer, the Ko D pellets appeared to stay intact during release, while a few grains were seen to detach from the pellets of both Ko-h D and Ko P samples after 6 h in pH 1. The Alg-G P and Alg-M P pellets (not shown in the figure) formed a single piece of what appeared to be an alginate gel precipitate during release [16]. The alkaline geopolymer synthesis conditions most likely give rise to an initially higher local pH inside the pellet pores [17] during the first stages of release. Thus, a pH gradient, directed inwards from the pellet surface and reaching a maximum value immediately after penetration of the release media into the pellet, most likely exists. The higher pH inside the pellets allows for dissolution of the Alginate polymer, which starts to diffuse concomitantly with the drug. After the maximum pH gradient is reached, the pH inside the pellets is expected to decrease with time as the buffer protons diffuse into the pellet, reaching the dissolved alginate polymer that re-precipitates.

Fig. 2c and d shows the release of Zolpidem from the geopolymer pellets in pH 1 and pH 6.8, respectively. The release curve for PEG-h D is not shown in Fig. 2c since it almost completely overlays the release curve for PEG D. Only the samples from which the Zolpidem release was slower than for the Control sample were tested in pH 6.8. Thus, the samples containing PEG are not shown in Fig. 2d.

The two release medias were used to mimic the pH condition of the stomach (the pH in the stomach can be as low as 1) and gastrointestinal tract, respectively. The Control sample released its entire drug content within 4–5 h in pH 1, Fig. 2c, and about 70% of its drug content within 24 h in pH 6.8, Fig. 2d, in accordance with what has been observed earlier for Zolpidem release from pure geopolymer samples [5]. As mentioned in the

Introduction, the more rapid release in pH 1, as compared to pH 6.8, can be partly explained by the higher solubility of the weak base drug at lower pH and partly by the degradation of the geopolymer under acidic conditions [5]. In Fig. 2b it was shown that the Control sample pellets turned into grains in the dissolution vessel during release in pH 1. However, the pellets containing methacrylic acid/ethyl acrylate copolymer or alginate appeared intact, and also released their Zolpidem drug load at a considerably slower rate (Fig. 2c). The polymer, thus, reinforced the pellet matrix, in combination with introducing an insoluble excipient in the pore structure, and enabled it to act as a diffusion barrier against immediate drug release or dose dumping, i.e. rapid and unintended release of the entire dose from a sustained release drug vehicle [18]. In line with this reasoning, the Ko D sample, having the most well dispersed polymer in the pellet matrix according to observations made using SEM (Fig. 1), was also delaying drug release the most (Fig. 2c) because of its ability to preserve the pellet shape during release in low pH. Decreasing the polymer concentration to a half (Ko-h D), lead to an increased drug release rate in pH 1, Fig. 2c. Using powder, instead of pre-dissolved polymer in the pellet synthesis, impaired the polymer dispersion, as seen in SEM (Fig. 1d), which also resulted in an increased drug release rate in pH 1 (compare Ko D and Ko P in Fig. 2c). Interestingly, because the solubility of PEG is not pH sensitive (Table 1), it dissolves well in both acidic and more neutral environments, allowing the pore network to open up during dissolution and leading to a faster release of Zolpidem than from the other pellets under study (Fig. 2c). Although Alginate appeared less well-dispersed in the pellets (Fig. 1e and f) compared to Kollicoat powder (Fig. 1d), the Alginate containing pellets released Zolpidem at a slower rate than Kollicoat containing ones. This is most probably related to the different polymers ability to dissolve, diffuse and re-precipitate during release, which is also the likely explanation for the difference in release rate between the alginate polymers consisting of higher ($G_c \approx 70\%$, Alg-G) and lower ($G_c \approx 30\%$, Alg-M) amounts of guluronic acid. Apart from reinforcing the geopolymer pellet matrix, the anionic Alginate polymer may also interact with the cationic Zolpidem (pK_a 6.4) via electrostatic interactions, thus, causing differences in the Zoldipem release rate from the two different Alginate containing samples.

Even though both Ko and Alg powders acted as pore formers by inducing micrometer sized voids in the pellet structure (Fig. 1), all pellets containing polymer excipients that were analyzed in pH 6.8 released less or the same amount of drug in 24 h at this pH as compared to the Control sample, Fig. 2d. Since the geopolymer is inert at pH 6.8 [10], the dissolved polymer is hindered from diffusing out, and might consequently restrain the drug by partially clogging the native geopolymer pores probably in combination with formation of a polymer film in the pore structure. The observed differences in release rate at pH 6.8 between the compositions under study are, thus, most likely caused by the varying capability of the tested polymers to sterically and electrostatically interact with the drug on its diffusive motion out of the pellet matrix.

In addition to the polymers listed in Table 1, the polymer excipient Eastmam Cellulose Acetate Phthalate was also tested. Pellets containing Cellulose Acetate Phthalate did not differ significantly in their release behavior of Zolpidem compared to Control samples.

4. Summary and conclusions

Pellets made from one geopolymer formulation with the commercially available polymer excipients methacrylic acid/ethyl acrylate copolymer, PEG and Alginate were prepared containing the sedative drug Zolpidem, herein acting as a model drug for the highly potent opioid Fentanyl. Scanning electron microscopy, compression strength tests and drug release experiments (in pH 1 and 6.8) were performed. The SEM micrographs showed that the polymer excipients were well dispersed in the pellet microstructure when they were dissolved prior to synthesis, but induced micrometer-sized voids when added in powder form or PEG in solution. The high compression strength of the pure geopolymers was maintained after addition of pre-dissolved polymer excipients during synthesis, whereas it decreased somewhat for geopolymers with polymers added in powder form. The maintained mechanical stability of the geopolymer structure after addition of excipients is a prerequisite to hamper dose dumping via voluntary or in-voluntary pellet crushing.

The drug release rates in pH 1 decreased for compositions containing polymer excipients as compared to the corresponding rate for a pure geopolymer Control sample, except for pellets containing PEG. The polymer excipients in the geopolymer pellets were anticipated to have several roles during drug release. The major role was probably to retain a barrier towards drug diffusion and release by keeping the pellet together in pH 1. Apart from also acting as a pore-forming agent, it might have provided additional ion-exchange sites for the charged drug molecules to further delay release in pH 1. Drug releases in pH 6.8 from pellets with polymer excipients were slower or comparable to release from the Control sample. The reduced drug release rate at pH 6.8 may be due to a clogging behavior of the dissolved polymer excipients, probably in combination with formation of a polymer film in the pore structure, hindering drug diffusion in the native geopolymer pores in the inert matrix.

Improving acid resistance while retaining mechanical stability of geopolymers are crucial for being able to introduce such materials as delivery vehicles for sustained and safe oral delivery of highly potent opioids to the market. The results presented in this work, together with those in a recent study on the influence of drug distribution and solubility on release from geopolymers [19], open up the possibility to create safe, oral, one-tablet-a-day systems to treat chronic pain.

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